VERIZONA PUBLISHER
Publishing Your Ideas

www.verizonaonlinepublishing.com
Vol: 1, Issue: 3

Food and Nutrition Report

Does the Existence of Senolytic Compounds Underpin that Anti-Senolytics May Exist? A view on the Heaven and Hell of Cellular Senescence

Marco Malavolta[1*] and Mauro Provinciali[2]

[1]Nutrition and aging Centre, Scientific and Technological Area, Italian National Institute of Health and Science on Aging (INRCA)

[2]Advanced Technology Center for Aging Research, Scientific TechnologicalArea, Italian National Institute of Health and Science on Aging (INRCA), Italy

***Corresponding author:** Dr. Marco Malavolta (PhD) Nutrition and aging Centre, Scientific and Technological Area, Italian National Institute of Health and Science on Aging (INRCA), Italy; Tel: +39-071-8004116; Fax: +39-071-206791; E-mail: m.malavolta@inrca.it

Article Type: Opinion, **Submission Date**: 8 June 2016, **Accepted Date**: 22 July 2016, **Published Date**: 30 August 2016.

Citation: Marco Malavolta and Mauro Provinciali (2016) Does the Existence of Senolytic Compounds Underpin that Anti-Senolytics May Exist? A view on the Heaven and Hell of Cellular Senescence. F Nutr Reprt 1(3): 31-34.

Abstract

The discovery of compounds that can selectively target senescent cells (called senolytic compounds) has moved lot of research around this new field of development ofdrugs and nutraceutical compounds. The promises, expectations and innovations in the therapy of age-related pathologies characterized by an increased low grade chronicinflammatory status [which is likely driven in part by the senescence- associated secretoryphenotype (SASP) produced by accumulating senescent cells] are so high that we are tempted to describe this field as a new scientific "Heaven". However, if this Heaven is real, that might seem to suggest that Hell is also real. In this case the term "Hell" refers not only to the potential side-effects of senolytic compounds and to the pro-senescence effects displayed by other compounds, but also to the possibility that real "anti-senolytics" exist. We cannot exclude that among common drugs (in particular those associated with chronic side-effects in elderly) or natural bioactive compounds there are molecules able to promote resistance to apoptosis in senescent cells, or able to depress senescence immunesurveillance thus promoting accumulation of senescent cells. Comparing differential effects of drugs and bioactive compounds in senescent versusnormal cells could ameliorate the development of drugs and nutraceuticals tailored to the needs of elderly people.

Keywords: Cellular senescence, Senolytics, Immune surveillance, Senescent cells.

Introduction

In the last two years a new term has been introduced in scientific literature: "senolytic agents" (or "senolytic compounds". This term was coined to describe natural or synthetic compounds that can selectively kill senescent cells without any dramatic effect on normal proliferating and terminally differentiated cells [1]. The discovery that a common anticancer drug, desatinib, and a well-known flavonol, quercetin, can display senolytic activity on senescent pre-adipocytes and endothelial cells, respectively, was immediately followed by the discovery of additional senolytic compounds, thus reinforcing the idea that this could be acomplete new field of development of drugs and nutraceutical compounds. Most of these compounds appears to act as inhibitors of Bcl-2 family member proteins. ABT263 (a specific inhibitor of the antiapoptotic proteins Bcl-2 and Bcl-xL), can induce apoptosis in various senescent cells, including senescent bone marrow hematopoietic stem cells and senescent muscle cells [2]. Navitoclax, which targets Bcl-2, Bcl-xl, and Bcl-w, was shown to be senolytic for senescent endothelial cells and fibroblasts [1]. Other mechanisms on the basis of senolytic activity include the inhibition of glucose metabolism (e.g. byphloretin) and of the protein degradation pathways that have been found up regulated in various models of senescent cells [3]. Several other compounds, including natural bioactive compounds, have the potential to display senolytic activity thus raising the interest for the development of a new class of nutraceuticals. Reasonable senolytic candidates among nutritional compounds are those molecules displaying rejuvenating effects on senescent cells "in vitro", as this effect might be the consequence of the senolytic activity combined with a selective survival of a sub-population of non-senescent cells in the culture [4,5].

Rationale for the "Senolytic Heaven"

Although it is well recognized that cellular senescence is a beneficial phenomenon in the organism aldefense against cancer as well as in wound healing [6], control of fibrosis and tissue repair [7], the properuse of compounds that can remove excessive accumulation of senescent cells appears beneficial as well. Senescent cells display a particular chromatin configuration that stably silence proliferation-promoting genes while simultaneously activates the SASP program. One of the functions attributed to the SASP is to attract immune cells, which in turn can coordinate the elimination of senescent cells. However, the SASP is suspected to promote aged pheno type of tissues as well as chronic inflammation and even the development of a pro-tumorigenic microenvironment [8].

The rationale under the development of senolytic compounds lies in the concept that senescent cells accumulate excessively in organs and tissues during aging, thus contributing to the physiological decline and pathological changes [9–11]. These observations have led to the idea that physiological mechanisms that are deputed to the clearance of senescent cells can be affected by aging. The age-associated alterations of the immune system can contribute to impair the organism's ability to clear-off senescent cells. Moreover, there is also evidence that most senescent cells can develop resistance to apoptosis, so that some researchers are currently considering them like "non-proliferating cancers". This fact may be consequent to epigenetic changes occurring in cells during individual life span that cause intrinsic modifications in senescent cells, leading to phenotypic diversification and selection of senescent cells resistant to immune system clearance [12]. Most importantly, genetic based strategies to remove the excesses of senescent cells from the organism have been proven to rejuvenate tissues and extend lifespan in laboratory mice [13,14]. These beneficial results have been also confirmed with the administration of senolytic compound in murine models "in vivo"[1,2,15].

Hypothesis on the "Anti-Senolytics Hell"

Based on this concept, lots of studies are currently under way looking at cellular senescence as an innovative target for the major diseases and chronic conditions associated with aging. This new field of research promises expectations and innovations in the therapy of sarcopenia, type 2 diabetes, immune system decline and cardiovascular diseases as well as in all age-related pathologies characterized by an increased low grade chronic inflammatory status (which is likely driven in part by the SASP produced by accumulating senescent cells). The enthusiasm expressed around the development of senolytic compounds is quite like the discovery of a scientific "Heaven". However, if this Heaven is real, that might seem to suggest that Hellis also real. In this case the term "Hell" refers to those negative implications that arise from the concept that "compounds that eliminate accumulating senescent cells are good". The first of these inauspicious consideration is that side effects associated with certain drugs or bioactive compounds can arise from apromotion of accumulating senescent cells. For example, accelerated aging and long-term complications after cancer therapy are the likely consequence of extensive senescence induction in off-targets healthycells [16]. However, there are several other compounds which display side effects likely associated toinduction of senescence. Very recently, accelerated endothelial senescence has been claimed as a potential mechanism to explain the cardiovascular, renal and neurological morbidity associated with proton pump inhibitors use [17]. The poor knowledge around effects on normal cells and potential side effects of senoltyics also deserve particular care. Scientific research is currently in the stage of basic and pre-clinical testing of these compounds. It is necessary to urgently intensify the laboratory work "in vitro" as well as "pre-clinical" studies in laboratory mice in order to check potential senolytic activities of natural and synthetic compounds, as well as to verify their effects using models "in vivo". Indeed, senolytic treatments may affect the beneficial role of senescent cells in tissue repair [12] and, importantly, there may be other unidentified advantageous effects of senescence, especially in humans [18]. Another lack of knowledge regards the possibility that certain drugs (in particular those associated with chronic or severe side-effectsin elderly) or natural bioactive compounds may be able to protect senescent cells from apoptosis or, to depress senescence immune surveillance ("anti-senolytic" activity) thus promoting accumulation of senescent cells. These compounds may exert their activity by favoring the process of dysregulation of apoptotic pathways on newly formed senescent cells by a process similar to the one identified for volatile anesthetics and dexamethasone in certain cancer cellular models [19,20]. It has been shown that young and senescent cells can respond differently to treatment with cytokines (e.g. IFN-γ) [21], natural bioactive compounds (e.g. rotenone) [22], and common drugs (e.g. proton pump inhibitors) [17].

Some drugs (e.g. glucocorticoids), and natural bioactive compounds (e.g. resveratrol) have been studied fortheir capacity to decrease the production of SASP components in human senescent cells [23,24]. This effect generally consists of a reduced gene expression and release of pro-inflammatory cytokines, thus suggesting a potential beneficial improvement of tissue maintenance and repair. However, considering the original nature of SASP to attract immune cells for senescence immune surveillance, it would be important to of senescent cells thus hampering long term positive beneficial effects. In the case of glucocorticoids, this class of compounds may induce senescence [25], prevent apoptosis with mechanisms involving upregulation of Bcl-xL [26], suppress the SASP [27], and have been associated with immunosenescence [28], thus suggesting a deleterious impact on senescence immune surveillances. Hence, it would not be surprising to find out that part of side effects associated with long term use of glucocorticoids (e.g in patients with asthma or chronic respiratory diseases) are the consequence of accumulating senescent cells. Additional pharmacological and nutritional compounds that can modulate the function of regulatory T (Treg) cells and myeloid derived suppressor cells (MDSCs) [29,30], could also play a role in suppression of immune surveillance of senescent cells. Unfortunately, there are still no focused studies in this area and the effects of long term administration of immunomodulatory compounds (including natural bioactive compounds and probiotics) in the accumulation of senescent cells are still unknown. It should be also mentioned that an high fat diet, which appears a likely candidate among nutritional anti-senolytics, was shown to not induce accumulation of senescent cells in the p16ink4a reporter mice [31].

In conclusion, given that senescent cells accumulate in old tissues, find out a possible anti-senolytic activityof drugs and natural bioactive compounds would be helpful to predict potential hazard of their long termuse in elderly and even in younger people. A description of the mechanism that deserve particular attention in this field could be retrieved from Figure 1.

Future Perspective

While most gene expression studies have been addressed to identify differences between normal and senescent cells, few studies have been focused to identify differences in gene expression response to drugsor natural bioactive compounds. There is urgent need to intensify these studies in order to ameliorate the development of drugs targeted to the need of elderly people. These studies should be flanked by others focused on the mechanisms

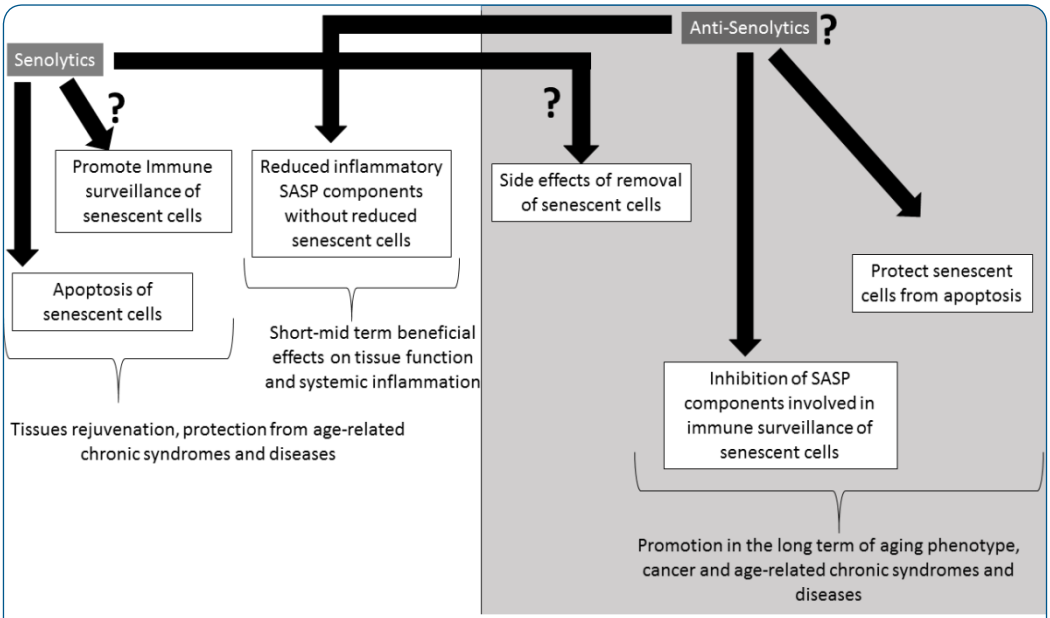

Figure 1: Activity of seneolytics and putative targets of anti-senoltyics. On the left side (in white background) beneficial effects of senoltycs and possible short-term positive effects of anti- senolytics (the «Senolytic Heaven»). On the right side (in grey background) deleterious effects of anti- senoltycs and possible deleterious effects of senolytics (the «Senolytic Hell»).

of accumulation of senescent cells "in vivo" using newly developed transgenic mouse models that allows to visualize, isolate and eliminate senescent cells [6] and including an important focus on senescence immune surveillance. Increasing knowledge around the mechanisms that drive accumulation of senescent cells during therapy may help scientists to ameliorate pharmacological and nutritional therapies in elderly.

Refernces

1. Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell. 2015; 14(4):644–58. doi: 10.1111/acel.12344.
2. Jianhui Chang, Yingying Wang, Lijian Shao, Remi-Martin Laberge, Marco Demaria, Judith Campisi, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med. 2016; 22:78–83.doi:10.1038/nm.4010.
3. Dörr JR, Yu Y, Milanovic M, Beuster G, Zasada C, Däbritz JH, et al. Synthetic lethal metabolic targeting of cellular senescence in cancer therapy. Nature. 2013; 501(7467):421–5.doi: 10.1038/nature12437.
4. Malavolta M, Pierpaoli E, Giacconi R, Costarelli L, Piacenza F, Basso A, et al. Pleiotropic Effects of Tocotrienols and Quercetin on Cellular Senescence: Introducing the Perspective of Senolytic Effects of Phytochemicals. Curr Drug Targets. 2016; 17(4):447–59.
5. Provinciali M, Pierpaoli E, Piacenza F, et al. Chapter 22 – Nutritional Modulators of Cellular Senescence In Vitro. In: Molecular Basis of Nutrition and Aging. 2016; 293–312 p.
6. Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell. 2014; 31(6):722–33.doi: 10.1016/j.devcel.2014.11.012.
7. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol. 2014; 15(7):482–96. doi: 10.1038/nrm3823.
8. Coppé J-P, Desprez P-Y, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010; 5:99–118.doi: 10.1146/annurev-pathol-121808-102144.
9. Sousa-Victor P, Gutarra S, García-Prat L, Rodriguez-Ubreva J, Ortet L, Ruiz-Bonilla V, et al. Geriatric muscle stem cells switch reversible quiescence into senescence. Nature. 2014; 506(7488):316–21.doi: 10.1038/nature13013.
10. Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, et al. Ink4a/Arf expression is a biomarker of aging. J Clin Invest. 2004; 114(9):1299–307.
11. Ohtani N, Yamakoshi K, Takahashi A, Hara E. Real-time in vivo imaging of p16gene expression: a new approach to study senescence stress signaling in living animals. Cell Div. 2010; 5:1.doi: 10.1186/1747-1028-5-1.
12. van Deursen JM. The role of senescent cells in ageing. Nature. 2014; 509(7501):439–446. doi: 10.1038/nature13193.
13. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016; 530(7589):184–9.doi: 10.1038/nature16932.
14. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011; 479(7372):232–6.doi: 10.1038/nature10600.
15. Roos CM, Zhang B, Palmer AK, Ogrodnik MB, Pirtskhalava T, Thalji NM, et al. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. Aging Cell. 2016. doi: 10.1111/acel.12458.
16. Roninson IB. Tumor cell senescence in cancer treatment. Cancer Res. 2003; 63(11):2705–15.
17. Yepuri G, Sukhovershin R, Nazari-Shafti TZ, Petrascheck M, Ghebre YT, Cooke JP. Proton Pump Inhibitors Accelerate Endothelial Senescence. Circ Res. 2016; 118(12):e36-42.doi: 10.1161/CIRCRESAHA.116.308807.

18. Triana-Martínez F, Pedraza-Vázquez G, Maciel-Barón LA, Königsberg M.Reflections on the role of senescence during development and aging. Arch Biochem Biophys. 2016; 598:40–9.doi: 10.1016/j.abb.2016.04.004.

19. Kawaraguchi Y, Horikawa YT, Murphy AN, Murray F, Miyanohara A, Ali SS, et al. Volatile anesthetics protect cancer cells against tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis via caveolins. Anesthesiology. 2011; 115(3):499–508.doi: 10.1097/ALN.0b013e3182276d42.

20. Petrella A, Ercolino SF, Festa M, Gentilella A, Tosco A, Conzen SD, et al. Dexamethasone inhibits TRAIL-induced apoptosis of thyroid cancer cells via Bcl-xL induction. Eur J Cancer. 2006; 42(18):3287–93.

21. Stratford FLL, Chondrogianni N, Trougakos IP, et al. Proteasome response to interferon-gamma is altered in senescent human fibroblasts. FEBS Lett. 2006; 580(16):3989–94.

22. Marthandan S, Priebe S, Groth M, Guthke R, Platzer M, Hemmerich P, et al. Hormetic effect of rotenone in primary human fibroblasts. Immun Ageing. 2015; 12:11.doi: 10.1186/s12979-015-0038-8.

23. Malavolta M, Costarelli L, Giacconi R, Piacenza F, Basso A, Pierpaoli E, et al. Modulators of cellular senescence: mechanisms, promises, and challenges from in vitro studies with dietary bioactive compounds. Nutr Res. 2014; 34(12):1017–35.doi: 10.1016/j.nutres.2014.02.006.

24. Pitozzi V, Mocali A, Laurenzana A, Giannoni E, Cifola I, Battaglia C, et al. Chronic resveratrol treatment ameliorates cell adhesion and mitigates the inflammatory phenotype in senescent human fibroblasts. J Gerontol A Biol Sci Med Sci. 2013; 68(4):371–81.doi: 10.1093/gerona/gls183.

25. Poulsen RC, Watts AC, Murphy RJ, Snelling SJ, Carr AJ, Hulley PA. Glucocorticoids induce senescence in primary human tenocytes by inhibition of sirtuin 1 and activation of the p53/p21 pathway: in vivo and in vitro evidence. Ann Rheum Dis. 2014; 73(7):1405–13. doi: 10.1136/annrheumdis-2012-203146.

26. Nieuwenhuis B, Lüth A, Kleuser B. Dexamethasone protects human fibroblasts from apoptosis via an S1P3-receptor subtype dependent activation of PKB/Akt and Bcl XL. Pharmacol Res. 2010; 61(5):449–59.doi: 10.1016/j.phrs.2009.12.005.

27. Laberge RM, Zhou L, Sarantos MR, Rodier F, Freund A, de Keizer PL, et al. Glucocorticoids suppress selected components of the senescence-associated secretory phenotype. Aging Cell. 2012; 11(4):569–78. doi: 10.1111/j.1474-9726.2012.00818.x.

28. Bauer ME, Moriguchi Jeckel CM, Bonorino C, et al. Glucocorticoids and DHEA: Do They Have a Role in Immunosenescence? In: Handbook on Immunosenescence. Dordrecht Netherlands: Springer; 833–862 p.

29. Parker KH, Beury DW, Ostrand-Rosenberg S. Myeloid-Derived Suppressor Cells: Critical Cells Driving Immune Suppression in the Tumor Microenvironment. Adv Cancer Res. 2015; 128:95–139.doi: 10.1016/bs.acr.2015.04.002.

30. Issazadeh-Navikas S, Teimer R, Bockermann R. Influence of dietary components on regulatory T cells. Mol Med. 2012; 18:95–110.doi: 10.2119/molmed.2011.00311.

31. Sorrentino JA, Krishnamurthy J, Tilley S, Alb JG Jr, Burd CE, Sharpless NE. p16INK4a reporter mice reveal age-promoting effects of environmental toxicants. J Clin Invest. 2014; 124(1):169–73.doi: 10.1172/JCI70960.